REMARKS

Claims 68-81, 84-95 and 107-132 are pending. Claims 78 and 92-95 have been amended. Claims 82, 83 and 96-106 have been cancelled. New claims 108-132 have been added. Support for the new claims can be found throughout the application as originally filed. No new matter has been added.

Claim Objections

The Examiner has objected to claims 92-95 as containing informalities. These claims have been amended to thereby obviate this objection.

Rejections under 35 USC § 112, first paragraph.

Claims 82-107 are rejected under 35 U.S.C. § 112, ¶ 1, as the specification, which is "enabling for the specific deposited PSMA antibodies E99, J415, J533, and J591, does not reasonably provide enablement for any antibody which binds the epitope bound by E99, J415, J533, and J591, or antibodies having variant or altered sequences." According to the Examiner, "[t]he specification fails to disclose specific guidance or working examples with regard to epitope mapping, or variations of the specific sequences of the disclosed antibodies." Office Action, page 3. The Examiner goes on to state "[e]pitope mapping and alterations of antibody structure are known to be complex and unpredictable. With regard to claims drawn to antibodies which bind to the epitope bound by antibodies E99, J415, J533, and J591, it would require undue experimentation to select and screen for these antibodies." The Examiner further states that "[t]he specification teaches a competitive binding assay of the antibodies E99, J415, J533, and J591 ..."

Office Action, pages 4-5. The portion of the rejection relating to epitope binding is overcome by canceling the claims and adding new claims.

Claims 82 and 83 directed to antibodies which recognize the epitope of J591, J533, J415 and E99 have been cancelled. New claim 108, and its dependencies, recite methods of detecting

normal, benign hyperplastic, or cancerous prostate cells in a subject using antibodies or antigen binding portions thereof which compete for binding to PSMA with a monoclonal antibody selected from the group consisting of E99, J415, J533, and J591.

The application clearly provides sufficient guidance such that a skilled artisan could make and use the antibodies as currently claimed without undue experimentation. Applicant has taught methods of making anti-PSMA antibodies and methods of testing anti-PSMA antibodies to determine if they compete for binding with the specified antibodies as required in the claims.

For instance, Example 3 of the application at page 36, line 33 – page 37, line 18, teaches a skilled artisan how to generate antibodies against PSMA. Briefly, female BALB/c mice were immunized peritoneally three times at two week intervals with LNCaP cells, which express high levels of PSMA on the surface. A final booster with cultured fresh prostate epithelial cells was administered, and three days later spleen cells from the immunized mice were fused with SP-2 mouse myeloma cells to form hybridomas. Several rounds of screening followed by subcloning by limiting dilution resulted in the isolation of the monoclonal antibodies disclosed herein.

The claimed antibodies are required to compete with a monoclonal antibody selected from the group of E99, J415, J533 and J591. Each of these four monoclonal antibodies has been deposited and is thus available to one of ordinary skill in the art. A skilled artisan could use art known methods together with the specific antibodies which have been made publicly available to determine if a candidate antibody meets the competition limitation. For example, the artisan could follow the protocol set out in Example 10 of the specification which teaches a competition assay. Page 42, line 17 – page 44 line 4 of the present application. Thus, a skilled artisan, following the guidance provided by the application, using routine methods and publicly available reagents, could produce an antibody that competes for binding with any one of J415, J591, J533 and E99 without undue experimentation.

The Examiner further asserts that "the specification fails to disclose specific guidance or working examples with regard to ... variations of the specific sequences of the disclosed antibodies including CDR grafting and engineering of the claimed antibodies." In particular, the Examiner states that:

> [W]ith regard to claims which recite antibodies which minimally contain "binding portions" of various antibody regions (claims 84-95), it is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function ... It is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of the E99, J415, J533, and J591 antibodies, in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function.

Applicant respectfully traverses the Examiner's statement regarding the lack of enablement for antibodies having altered or variant sequences. As noted by the Examiner, at the time of the invention, much was known in the art regarding the structure and function of antibodies. The state of the art referred to by the Examiner actually supports enablement. E.g., the Examiner discusses the role of heavy and light chains and CDR's in maintaining antibody function. This is in fact guidance for one who would make antibodies of the invention. A skilled artisan would have been able to make and use a wide variety of antibodies and antigen binding fragments which retain antigen binding capability without undue experimentation.

For example, numerous methods were known in the art for producing functional antibodies or antigen-binding fragments thereof with variant sequences. For instance, various methods for humanizing antibodies produced in mice were known at the time of the invention. To highlight just a few, Queen et al, *Proc Natl Acad Sci U S A.* 1989 Dec;86(24):10029-33, teach antibodies humanized by combining the CDRs of a mouse antibody with human framework and constant regions; EP 0 328 404 teaches replacing the CDRs of human antibodies with those from a mouse; Riechmann et al., *Nature* 1988 Mar 24;332(6162):323-7, teach human antibodies reshaped by introducing the hypervariable regions from a rat monoclonal antibody; EP 0 403 156 teaches "civilized" antibodies created by mutating residues in mouse antibody variable regions to the human sequence and expressing them with human constant regions. U.S. Patent No.

5,225,539 to Winter et al. discloses methods for producing altered antibodies by replacing the CDRs of a variable region of an Ig with the CDRs from an Ig of different specificity, using recombinant DNA techniques. Thus, in view of the knowledge in the art and the information provided in the present application, a skilled artisan could produce a wide variety of anti-PSMA antibodies without undue experimentation. The use of fragments or portions of antibodies was also known in the art at the time of the invention. See, e.g., page 23 of the present application.

The Examiner further argues that antibodies having other than the specific constellation of CDR's from E99, J415, J591 or J533 would not have the required binding function. Applicant respectfully traverses this portion of the rejection. The Examiner has provided no reason at all to believe that immunization as described in the present application would not produce antibodies with the claimed properties which have CDR's other than those of E99, J415, J533, and J591. Four different antibodies were made and disclosed in the application - - the Examiner provides no scientific basis for believing they are the only ones that could be made when the immunization and selection protocols provided by the Applicant are followed. Thus, the specification teaches one how to make antibodies of the invention other than those recited in the examples. In addition, the specification, together with art-known knowledge, allows one to use antibodies like E99, J415, J533 and J591 to make variants such as CDR grafted or humanized antibodies.

The Examiner cites Panka et al. for the proposition that alterations of a single amino acid residue can alter antigen-binding affinity. First, the claims do not require that all antibodies of the claim have the same affinity as the recited examples. Second, Panka et al. were looking for variants with altered binding properties, and describe the use of two-color FACS for doing so. The variant discovered by Panka et al is a serine-to-arginine mutation in the variable region of the antibody. Such a mutation, which is not considered a conservative mutation, might be expected to have such a result. This does not mean that one of skill in the art would be unable to produce variants of the claimed antibodies with altered sequences that retain the antigen-binding properties of the parent molecule. For instance, it was known that antibody variants made by conservative substitutions or substitutions in specific areas are less likely to affect antigen binding. Humanization, for example, replaces large numbers of donor antibody residues. Thus, the Panka et al. reference further demonstrates Applicant's point that the knowledge in the art

was at a high level. The art such as the CDR grafting and humanization references cited above demonstrate ways in which the art teaches how to make changes which do not destroy affinity.

The Examiner also cites Adair et al. as teaching that "transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product." In fact, Adair et al. teach a protocol for obtaining satisfactory CDR-grafted products regardless of the level of homology between the donor immunoglobulin and acceptor framework, see Adair, p. 6. The portion of Adair relied upon by the Examiner is the background in which a reference, Reichmann et al., is discussed. Adair et al. disclose that after CDR grafting it was found that an additional residue in the humanized antibody needed to be modified to enhance binding affinity. Adair et al. (and other references cited in the background of Adair et al.) then go on to provide protocols for designing humanized antibodies with binding activity. Thus, the Adair et al. reference, like the Panka et al. reference, provides another example of the amount of knowledge there was in the art at the time of filing regarding antibody structure and function.

The claims recite an "antigen binding portion" of an antibody. As admitted by the Examiner, it was well established in the art what portions of an antibody are needed to maintain binding capability. Therefore, given the guidance provided by the specification, the level of skill in the art, the level of knowledge regarding antibody structure and function, and the limitation of the claims to antibodies or antigen-binding portions thereof, it is clear that the claimed antibodies have been fully enabled.

Rejection Under 35 U.S.C. §102(e)

Claims 68-69, 77-79, 96, 98-100 and 107 are rejected under 35 U.S.C. §102(e) "as being anticipated by Murphy et al., US Patent 6,150,508." In particular, the Examiner states that "Murphy et al. ... teaches a method of detecting normal, benign, or cancerous prostate cells in a patient comprising providing an antibody or antigen binding portion thereof which binds to the extracellular domain of prostate specific membrane antigen ..."

The Applicant respectfully traverses this rejection. As discussed below, Murphy et al. is removed as prior art in light of the Declaration of Neil Bander, M.D. Under 37 CFR 1.131 (hereafter referred to as "the Bander declaration"), submitted herewith.

Murphy et al is not available as prior art against the present application because Applicant conceived and reduced the claimed invention to practice prior to the priority date of the Murphy et al patent. In particular, Murphy et al. has a priority date of March 25, 1996. As stated in the Bander declaration, Applicant conceived and reduced the claimed invention to practice prior to the priority date of the Murphy et al. patent. Therefore, Murphy et al is not available as prior art against the present claims.

Thus, Applicant respectfully requests that the Examiner withdraw this rejection.

Rejection Under 35 U.S.C. §103

Claims 68-79 and 96-107 are rejected under 35 U.S.C. §103 "as being unpatentable over Murphy et al., US Patent 6,150,508." In particular, the Examiner states that

> Murphy fails to teach the specific imaging techniques and antibody characteristics which are recited in the dependent claims ...These specific imaging techniques and antibody characteristics are well known in the art. ... Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the assays taught by Murphy et al., US Patent 6,150,508, and one would have been motivated to do so because these techniques are art recognized equivalents and variations for diagnosis and therapy.

The Applicant respectfully traverses this rejection. As discussed above, Murphy et al. is removed as prior art in light of the Declaration of Neil Bander, M.D. Under 37 CFR 1.131. Therefore, Applicant respectfully request that the Examiner withdraw this rejection.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed is a check for excess claim fees and a check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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Version with markings to show changes made

In the claims:

Claims 82, 83 and 96-106 have been cancelled.

Claims 78 and 92-95 have been amended as follows:

78. [Amended] A method according to claim 68, [wherein the antibody or antigen binding portion binds live cells and/or] wherein the antibody is an IgG.

92. [Amended] A method according to claim [241] 90, wherein the antibody or antigen binding portion thereof [which] comprises an antigen binding portion of an amino acid sequence encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO:6 (variable heavy chain) and SEQ ID NO:17 (variable light chain).

93. [Amended] A method according to claim 90, wherein the antibody or antigen binding portion thereof [which] comprises an antigen binding portion of an amino acid sequence encoded by a nucleic acid sequence from SEQ ID NO:6 (variable heavy chain) and an antigen binding portion of an amino acid sequence encoded by a nucleic acid sequence from SEQ ID NO:17 (variable light chain).

94. [Amended] A method according to claim 90, wherein the antibody or antigen binding portion thereof [which] comprises an antigen binding portion of an amino acid sequence encoded by a nucleic acid sequence selected from the group consisting of a nucleic acid sequence which encodes the variable heavy chain produced by the hybridoma having ATCC deposit no. HB-12126, and a nucleic acid sequence which encodes the variable light chain produced by the hybridoma having ATCC deposit no. HB-12126.

95. [Amended] A method according to claim 90, wherein the antibody or antigen binding portion thereof [which] comprises an antigen binding portion of an amino acid sequence

encoded by a nucleic acid which encodes the variable heavy chain produced by the hybridoma having ATCC deposit no. HB-12126 and an antigen binding portion of an amino acid sequence encoded by a nucleic acid which encodes the variable heavy chain produced by the hybridoma having ATCC deposit no. HB-12126.

New claim 108-128 have been added.

--108. [New] A method of detecting normal, benign hyperplastic, or cancerous prostate cells or a portion thereof in a human subject, comprising:

providing an antibody or antigen binding portion thereof which competes for binding to prostate specific membrane antigen with a monoclonal antibody selected from the group consisting of J591, J415, J533, and E99, wherein the antibody or antigen binding portion thereof is bound to a label effective to permit detection of normal, benign hyperplastic, or cancerous prostate cells or a portion thereof;

administering the antibody or antigen binding portion thereof to the human subject;

detecting the presence of the normal, benign hyperplastic, or cancerous prostate cells or a portion thereof by detecting the label.

109. [New] A method according to claim 108, wherein the antibody or antigen binding portion thereof competes for binding to prostate specific membrane antigen with monoclonal antibody J591.

110. [New] A method according to claim 108, wherein the antibody or antigen binding portion thereof competes for binding to prostate specific membrane antigen with monoclonal antibody J415.

111. [New] A method according to claim 68, wherein the antibody or antigen binding portion thereof binds to live cells.

112. [New] A method according to claim 68, wherein the antibody or antigen binding

portion thereof comprises an antigen binding portion of an amino acid sequence selected from the group consisting of an amino acid sequence of the variable heavy chain produced by the hybridoma having ATCC deposit no. HB-12109, and an amino acid sequence of the variable light chain produced by the hybridoma having ATCC deposit no. HB-12109.

113. [New] A method according to claim 68, wherein the antibody or antigen binding portion thereof comprises an antigen binding portion of an amino acid sequence of the variable heavy chain produced by the hybridoma having ATCC deposit no. HB-12109, and an amino acid sequence of the variable light chain produced by the hybridoma having ATCC deposit no. HB-12109.

114. [New] A method according to claim 68, wherein the antibody or antigen binding portion thereof comprises an antigen binding portion of an amino acid sequence encoded by a nucleic acid sequence selected from the group consisting of a nucleic acid sequence which encodes the variable heavy chain produced by the hybridoma having ATCC deposit no. HB-12109, and a nucleic acid sequence which encodes the variable light chain produced by the hybridoma having ATCC deposit no. HB-12109.

115. [New] A method according to claim 68, wherein the antibody or antigen binding portion thereof comprises an antigen binding portion of an amino acid sequence encoded by a nucleic acid which encodes the variable heavy chain produced by the hybridoma having ATCC deposit no. HB-12109 and an antigen binding portion of an amino acid sequence encoded by a nucleic acid which encodes the variable heavy chain produced by the hybridoma having ATCC deposit no. HB-12109.

116. [New] A method according to claim 68, 78, 84, 90, 108, or 111, wherein the antibody is a monoclonal antibody.

117. [New] A method according to claim 68, 78, 84, 90, 108, or 111, wherein the antibody or antigen binding portion thereof is internalized with the prostate specific membrane

antigen.

118. [New] A method according to claim 68, 78, 84, 90, 108 or 111, wherein the antibody or antigen binding portion thereof is selected from the group consisting of a Fab fragment, a $F(ab')_2$ fragment, and a Fv fragment.

119. [New] A method according to claim 68, 78, 84, 90, 108, or 111, wherein the label is selected from the group consisting of a fluorescent label, a biologically-active enzyme label, a radiolabel, a nuclear magnetic resonance active label, a luminescent label, and a chromophore label.

120. [New] A method according to claim 119, wherein the label is a radiolabel.

121. [New] A method according to claim 120, wherein the radiolabel is a short-range radiation emitter.

122. [New] A method according to claim 121, wherein the radiolabel is selected from the group consisting of ^{212}Bi, ^{213}Bi, and ^{211}At.

123. [New] A method according to claim 120, wherein the radiolabel is selected from the group consisting of ^{32}P, ^{125}I, ^{3}H, ^{14}C, and ^{188}Rh.

124. [New] A method according to claim 120, wherein the radiolabel is ^{131}I.

125. [New] A method according to claim 120, wherein the radiolabel is ^{99}mTc.

126. [New] A method according to claim 120, wherein the radiolabel is ^{111}In.

127. [New] The method according to claim 68, wherein the method is a method of detecting benign hyperplastic cells or a portion thereof in the subject.

128. [New] The method according to claim 68, wherein the method is a method of detecting cancerous prostate cells or a portion thereof in the subject.